Journal of Applied Pharmaceutical Science Vol. 10(02), pp 037-043, February, 2020
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2020.102006
ISSN 2231-3354

Antimicrobial evaluation and molecular properties prediction of pyrazolines incorporating benzofuran and pyrazole moieties

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ARTICLE INFO

Received on: 03/07/2019
Accepted on: 17/11/2019
Available online: 05/02/2020

Key words:
Pyrazoline, benzofuran, pyrazole, antimicrobial activities, drug-likeness, Lipinski rules.

ABSTRACT

A series of chalcones **3–5,** 1*H*-pyrazolines **6–8,** *N*-phenylpyrazolines **9–11,** and *N*-acetylpyrazolines **12–14** incorporating benzofuran and pyrazole moieties were synthesized and screened for their *in vitro* antimicrobial activity against some of pathogenic microorganisms. Among the screened compounds, **7** and **13** showed the most promising antibacterial activity against *Escherichia coli* (G^-). Compound **11** displayed broad spectrum antibacterial activity against *Bacillus subtilis* (G^+). Moreover, compounds **10** and **4** were found to be the most potent antifungal agent against *Candida albicans* and *Aspergillus niger*, respectively. Also, the molecular properties prediction and drug-likeness model score (DLS) of all the synthesized compounds were calculated by SwissADME and MolSoft websites, respectively. The two compounds **7** and **13** were found to be maximum DLS of 0.75 and 0.83, respectively.

INTRODUCTION

An antimicrobial is an agent that kills microorganisms or stops their growth. There are many types of antimicrobial drugs in the markets, e.g., penicillins, cycloserine, aminoglycosides, chloramphenicol, quinolones, tetracyclines, and glycopeptides, but the resistance of microorganisms to antimicrobial drugs by internal resistance or acquired resistance decreased the activities of these drugs. Therefore, the development of newer antimicrobial compounds for the treatment of the resistance of microorganisms has become a major objective of medicinal chemists

Literature survey revealed that substituted pyrazoline could act as anticancer, antiviral, antioxidant, anti-inflammatory, antimicrobial, antidepressant, antiprotozoal, and antidiabetic agents (Havrylyuk *et al*., 2016; Marella *et al*., 2013; Silva *et al*., 2018). Derivative **A** showed potent antibacterial profile against the tested Gram-positive [Minimal Inhibition Concentration (MIC) = 8 µg/ml] and Gram-negative (MIC= 32 µg/ml) bacterial strains (Sharma *et al*., 2010). Compound **B** exhibit good activities against *Staphylococcus aureus* [inhibition zone (IZ)= 21 mm] and *Candida albicans* (IZ = 24 mm) (Sharshira *et al*., 2012). Compound **C** exhibited the most potent antimicrobial activities against *S. aureus*, *Pseudomonas Aeruginosa*, and *C. albicans* with MIC= 3.12 µg/ml (Ahmad *et al*., 2016). Also, some drugs bearing a pyrazoline moiety in their structures, e.g., phenazone and propyphenazone have analgesic and antipyretic effects. Metamizole is a spasm reliever, fever reliever, and it has anti-inflammatory effects **(**Fig. 1**)**.

Further literature survey revealed that benzofuran or pyrazole moieties have been implemented as anticancer, antiviral, antioxidant, antimicrobial, anti-inflammatory, and antimalarial agents (Chand *et al*., 2017; Karrouchi *et al*., 2018; Shamsuzzaman *et al*., 2015). Moreover, the compound **D** bearing benzofuran and pyrazole moieties showed excellent antimicrobial activities for *Ralstonia solanacearum*, *Klebsiella pneumoniae*,

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Fusarium oxysporum and *Aspergillus flavus* (Lingaraju *et al*., 2017). Compound **E** bearing benzofuran and pyrazoline moieties exhibited excellent antimicrobial activities in comparison with the standard drug used (Rangaswamy *et al*., 2012) **(**Fig. 1**)**.

Based on above information and in continuation of our research program to find new potent antimicrobial and anticancer agents (Abd El-All *et al*., 2016; Abo-Ghalia *et al*., 2017; Al-Salem *et al*., 2017; Amr *et al*., 2018; El-Naggar *et al*., 2018; Elgemeie *et al*., 2008; Hafez *et al*., 2013; Hassan and Hafez, 2018; Hassan *et al*., 2019; 2015a; 2017a; 2018a; 2017b; 2015b; 2017c; 2015c; Kassem *et al*., 2019; Khatab *et al*., 2019; Moustafa *et al*., 2018; 2019; Naglah *et al*., 2017; 2013; Osman *et al*., 2014; 2009), a series of pyrazolines **6–14** incorporating benzofuran and pyrazole moieties have been synthesized to evaluate their antimicrobial activity against some of pathogenic microorganisms. Also, the calculation of the pharmacokinetic properties and drug-likeness of all compounds were studied.(Fig. 2)

MATERIALS AND METHODS

Antimicrobial activities

The synthesized compounds (Chalcones **3–5,** 1H-pyrazolines **6–8,** N-phenylpyrazolines **9–11,** *and* N-acetylpyrazolines **12–14**) were evaluated their in vitro

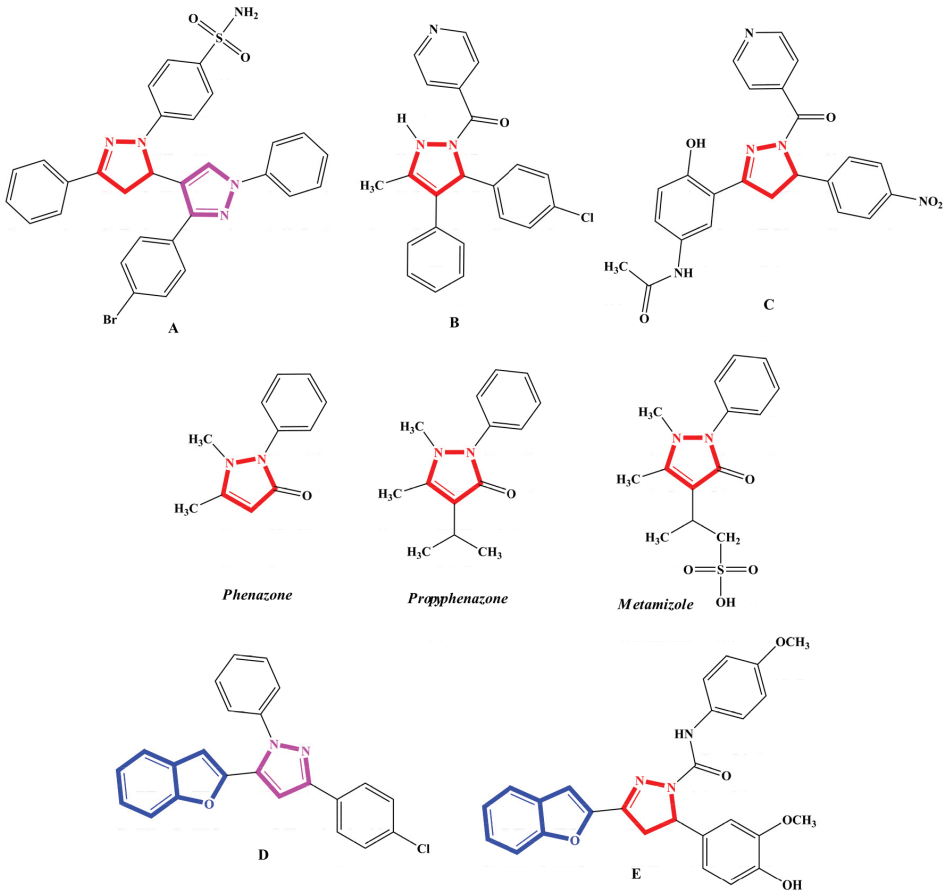


Figure 1. Examples of pyrazolines, benzofurans, and pyrazoles as antimicrobial activities and the structures of some drugs bearing pyrazoline moiety.

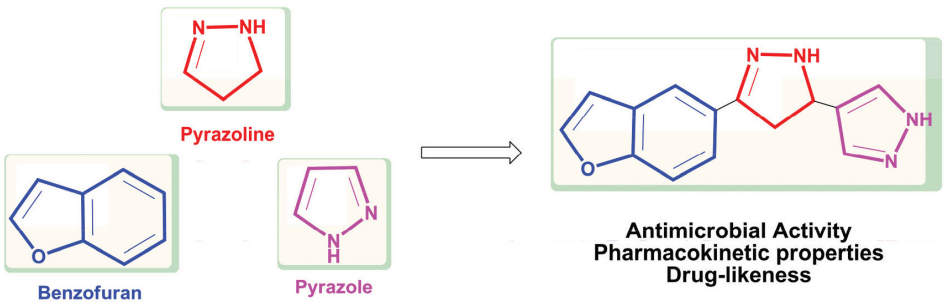


Figure 2. Design of pyrazoline derivatives incorporating benzofuran and pyrazole moieties.

antimicrobial properties against *Escherichia coli* (ATCC 25922), *Bacillus subtilis* (NRRL-B-4219), *Aspergillus niger* (ATCC 16888), and *C. albicans* (ATCC 10231) and comparison with antibiotic drugs (Negram, Vancomycin, and Nystatin) as standards by use of an agar well-diffusion method (MacLowry *et al*., 1970; Othman *et al*., 2011; Rocha *et al*., 1995; Valgas *et al*., 2007).

RESULTS AND DISCUSSION

Chemistry

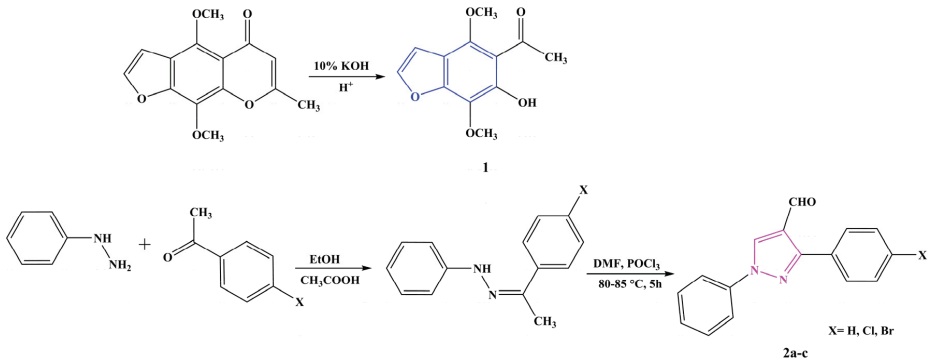
The starting materials [khellinone **1** (Osman *et al*., 2012) and 3-substituted-1-phenyl-1*H*-pyrazole-4-carbaldehydes **2a–c** (Jadhav *et al*., 2013)] were prepared according to the synthetic methods in Scheme 1.

The synthetic route used to synthesize the target series of pyrazolines incorporating benzofuran and pyrazole moieties is outlined in Scheme 2. Chalcones **3–5** have synthesized *via* the condensation of khellinone **1** with pyrazole aldehydes **2a–c**. Then, described a synthesis of 1*H*-pyrazolines **6–8**, *N*-phenylpyrazolines **9–11**, and *N*-acetylpyrazolines **12–14** *via* the cyclocondensation of **3–5** with hydrazine hydrate or phenyl hydrazine in refluxing ethanol or glacial acetic acid (Hassan *et al*., 2016) (Scheme 2).

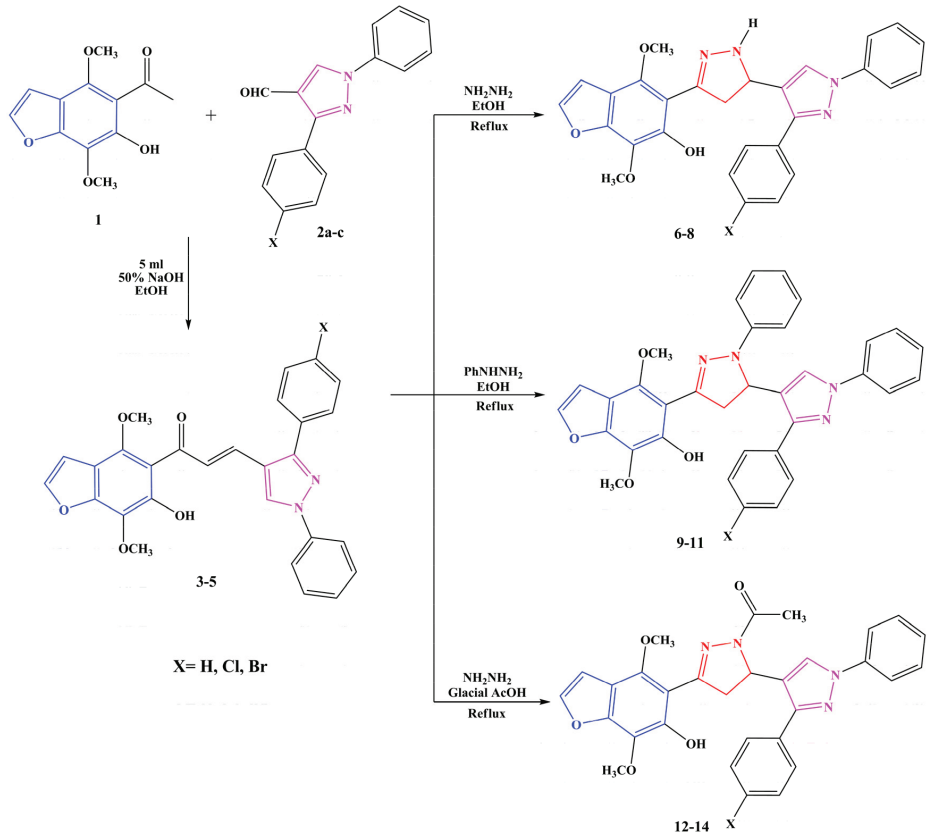
Biological evaluations

In vitro antimicrobial activity

The antibacterial and antifungal activities of the synthesized compounds **3–14** against a panel of pathogenic tested



Scheme 1. Synthesis of khellinone **1** and 3-substituted-1-phenyl-1*H*-pyrazole-4-carbaldehydes **2a–c**.



Scheme 2. Synthesis of 1*H*-pyrazolines **(6–8)**, *N*-phenylpyrazolines **(9–11)**, and *N*-acetylpyrazolines **(12–14)**.

organisms are represented in Table 1 and Figure 3. The results revealed that some synthesized derivatives exhibited excellent to moderate inhibitory effect.

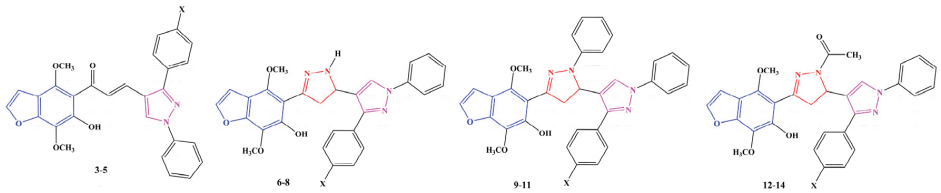
In case of *B. subtilis* (G+), compound **11** [inhibition zone (IZ) = 20 mm] recorded excellent inhibitory effect and equipotent to the antibacterial reference drug (Vancomycin, IZ = 21 mm). Compounds **(4, 7, 8, 9, 10, and 13)** showed a moderate inhibitory effect and recorded IZ diameter ranged from 12 to 16 mm. On the other hand, the rest of compounds **(3, 5, 6, 12, and 14)** did not show any inhibitory effect.

In case of *E. coli* (G-), the two compounds **7** and **13** (IZ = 20 mm) showed more potent inhibitory effect in comparison to the antibacterial reference drug (Negram, IZ = 16 mm). Compounds **(4, 9, 10, and 11)** showed activity (IZ rang = 14–15 mm) nearly equal to the activity of the antibacterial drug used (Negram, IZ = 16 mm), while the other tested compounds have not any inhibition effect.

By testing the compounds against *C. albicans*, compounds **(4, 7, 10, 11, and 14)** were more potent (IZ rang = 15–17 mm) than antifungal drug used (Nystatin, IZ = 14 mm). The two compounds **(5** and **8)** showed activity equal to antifungal drug used in this study (Nystatin, IZ = 14 mm). Also, the derivative **13** (IZ = 12 mm) showed a moderate inhibition effect.

In case of the pathogenic fungi, *A. niger*, compound **4** showed excellent inhibitory effect (IZ = 18 mm) more than (Nystatin, IZ = 15 mm). The four compounds **(3, 5, 10, and 11)** have activity equal to antifungal drug used (Nystatin, IZ = 15 mm).

Table 1. *In vitro* antimicrobial (inhibition zone of growth IZ, mm) of chalcones **3–5** and pyrazolines **6–14** against panel of pathogenic tested organisms.



Compounds	X	Bacteria		Fungi	
		B. subtilis (G^+)	*E. coli* (G^-)	*C. albicans*	*A. niger*
3	H	00	00	00	15
4	Cl	14	15	16	18
5	Br	00	00	14	15
6	H	00	00	00	00
7	Cl	13	20	16	00
8	Br	15	00	14	00
9	H	16	14	00	14
10	Cl	15	15	20	15
11	Br	20	15	17	15
12	H	00	00	00	00
13	Cl	12	20	12	00
14	Br	00	00	15	00
Negram		00	16	00	00
Vancomycin		21	00	00	00
Nystatin		00	00	14	15

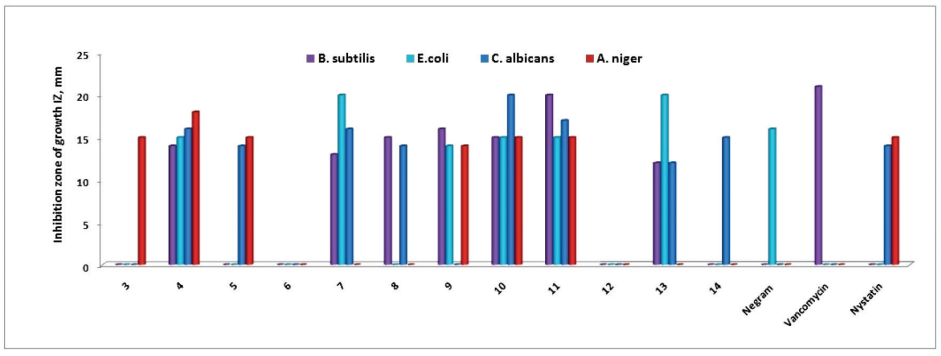


Figure 3. Antimicrobial activity of chalcones **3–5** and pyrazolines **6–14** against panel of pathogenic tested organisms.

Table 2. Lipinski's rule of five for the compounds, chalcones **3–5** and pyrazolines **6–14**.

Comp.	MW[a]	*M*LogP[b]	*n*HBA[c]	*n*HBD[d]	*n*RB[e]	$n_{violations}$ [f]
Rule	<500	≤4.15	≤10	≤5	≤10	0
3	466.48	2.43	6	1	7	0
4	500.93	2.90	6	1	7	1
5	545.38	2.99	6	1	7	1
6	480.51	2.53	6	2	6	0
7	514.96	2.99	6	2	6	1
8	559.41	3.09	6	2	6	1
9	556.61	3.73	6	1	7	1
10	591.06	4.18	6	1	7	2
11	635.51	4.27	6	1	7	2
12	522.55	2.47	7	1	7	1
13	557.00	2.93	7	1	7	1
14	601.45	3.03	7	1	7	1

[a] = Molecular weight, [b] = Calculated lipophillicity (MLog $P_{o/w}$), [c] = Number of hydrogen bond acceptor, [d] = Number of hydrogen bond donor, [e] = Number of rotatable bond (nRB), [f] = Violations from Lipinski's rule.

Table 3. Drug likeness calculations of the compounds, chalcones **3–5** and pyrazolines **6–14**.

Comp.	TPSA[a]	Volume[b]	%ABS[c] = 109 - (0.345 × TPSA)	DLS
3	69.19	461.51	85.13	-0.18
4	69.19	475.70	85.13	0.34
5	69.19	483.37	85.13	0.05
6	78.54	464.68	81.90	0.18
7	78.54	481.88	81.90	0.75
8	78.54	486.54	81.90	0.44
9	67.90	533.27	85.57	0.08
10	67.90	550.46	85.57	0.65
11	67.90	555.12	85.57	0.34
12	81.83	513.48	80.77	0.26
13	81.83	530.68	80.77	0.83
14	81.83	535.34	80.77	0.52

[a] = Topological polar surface area, [b] = Molecular volume, [c] = Percentage absorption.

Also, compound **9** (IZ = 14 mm) showed moderate activity. The compounds (**6–8** and **12–14**) have not any activity.

Finally, we recommend for using compounds **7** and **13** in the treatment of Gram-negative pathogenic microorganisms, compound **11** in the treatment of Gram-positive, compound **10** in the treatment of *C. albicans* and compound **4** in the treatment of *A. niger*.

Pharmacokinetic properties and drug-likeness

Lipinski's rule of five for the compounds, chalcones **3–5** *and pyrazolines* **6–14**

To qualify Chalcones **3–5** and pyrazolines **6–14** as a drug candidate, the molecular weight (MW), lipophilicity (MLogP), the number of hydrogen bond acceptors (*n*HBA), donors (*n*HBD), and the number of rotatable bond (*n*RB) of Lipinski's rule of five (Lipinski *et al*., 2001) were calculated using SwissADME web (http://swissadme.ch/index.php#undefined). The computed molecular properties are shown in Table 2.

Drug likeness calculations of the compounds, chalcones **3–5** *and pyrazolines* **6–14**

Molecular polar surface area (TPSA) is an affected parameter in the prediction of drug transport properties. Molecular volume was calculated by using the MolSoft website (http://molsoft.com/mprop/.). The percentage of absorption (%ABS) was calculated by using %ABS = 109 − (0.345 × TPSA) and referred to the degree of absorption (Desai *et al*., 2014).

Computed drug-likeness scores of the compounds, Chalcones **3–5** and pyrazolines **6–14** are presented in Table 3. Compound **3** has a negative value (DLS = −0.18) should not be considered as drug-like candidate. Compounds **7** and **13** possessed maximum drug-likeness model score (DLS) of 0.75 and 0.83, respectively.

CONCLUSION

In conclusion, we have synthesized a series of chalcones **3–5,** 1*H*-pyrazolines 6–8, *N*-acetylpyrazolines **12–14** 9–11, and *N*-acetylpyrazolines incorporating benzofuran and pyrazole

moieties. All the synthesized compounds were screened for their *in vitro* antimicrobial activity. The evaluations showed that compounds **4, 7, 10, 11,** and **13** were the most active compounds against a panel of pathogenic tested organisms. Also, the pharmacokinetic properties and calculation of drug likeness exhibited the two compounds **7** and **13** were found to be maximum DLS of 0.75 and 0.83, respectively.

ACKNOWLEDGMENTS

The authors wish to express their thanks to the National Research Centre for the facilities provided.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

FINANCIAL SUPPORT

None.

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How to cite this article:
Elsherif MA, Hassan AS, Moustafa GO, Awad HM, Morsy NM. Antimicrobial evaluation and molecular properties prediction of pyrazolines incorporating benzofuran and pyrazole moieties. J Appl Pharm Sci, 2020; 10(02):037–043.